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SUBSTANTIVE SPECIFICATION

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Inventors:
ADEOKUN, Miss Monisola,
AMBROSE, Dr Helen Jean,
CRESSWELL, Dr Carl John all British
and all of AstraZeneca, Alderley Park,
Macclesfield, Cheshire, GB-SK10 4TG
and
DUDLEY, Dr Adam Jeston,, Scientist
(British)
of AstraZeneca Pharmaceuticals,
1800 Concord Pike, Wilmington,
US-DE19850-5437;

TITLE:
CHEMICAL COMPOUNDS

APPLICANT:
AstraZeneca AB,
S-151 85 Södertälje, Sweden.

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CHEMICAL COMPOUNDS

This invention relates to polymorphisms in the human OATPC gene and corresponding novel allelic polypeptides encoded thereby. The invention also relates to methods and materials for analysing allelic variation in the OATPC gene, and to the use of OATPC polymorphism in treatment of diseases with OATPC transportable drugs.

Na+-independent organic anion transporting polypeptide (OATP) C gene is a member of the OATP supergene family involved in multifunctional transport of organic anion. OATPC tranports the organic anion taurocholate, conjugated steroids: DHEAS, estradiol 17β-D-glucoronide and estrone-3-sulfate, eicosanoids: PGE_2, thromboxane B_2, leukotriene C_4, and E_4, and thyroid hormones T4 and T3 [1,2]. OATPC has also been shown to be involved in the transport of xenobiotics, and drugs involved in lipid lowering *e.g.* statins[1]. Statins have been refered to as a first-line therapy for patients with atherosclerotic vascular diseases. The OATPC gene and its product is also thought to be of importance in other diseases due to its transport of DHEAS an adrenal steroid which has been suggested to have positive neuropsychiatric, immune, and metabolic effects[3]. Due to the substrate specificity, location in the liver, and being exclusively expressed in the liver, Abe *et al* suggested that OATPC could be the predominant clearance mechanism of several endogenous and exogenous substrates in the liver. OATPC is the first human molecule reported to transport thyroid hormones[2].

This liver specific transporter may be useful in liver-specific drug delivery systems and liver-specific chemotherapy, bile acid formation and the pathogenesis of diseases such as cholestasis, hyperbilirubinemia and thyroid hormone resistance.

The OATPC gene (sometimes called OAPT2 in the literature) has been cloned by four different groups, annotated and published as EMBL accession numbers AB026257 (OATPC, 2452bp), AF205071(OATP2, 2830, ref 1), AJ132573(OATP2, 2778)[4], and AF060500 (LST-

[1] A Novel Human Hepatic Organic Anion Transporting Polypeptide (OATP2), Hsiang *et al* J Biol Chem **274**, 37161-37168 (1999)

[2] Identification of a Novel Gene Family Encoding Human Liver-specifc Organic Anion Transporter LST-1, Takaaki Abe *et al* J Biol Chem **274**, 17159-17163 (1999)

[3] Bates *et al* (1998) Curr. Opin. Endocrinol. Diab. **5**, 357-366

[4] A novel human organic anion transporting polypeptide localised to the basolateral hepatocyte membrane, Konig Jorg *et al* (2000) Am J Physiol. Gastrointest. Liver Physiol. **278**: G156-G164